EXHIBIT C

DECLARATION UNDER 37 C.F.R. §1.132
OF JOE MILTON HARRIS

Docket No. SHE 10.12

Outside Counsel Ref. 34848/238257

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:

J. Milton HARRIS *et al.*		Examiner:	David M. NAFF
Serial No.:	10/119,546	Art Unit:	1651
Filed:	April 10, 2002		
Title:	**MULTI-ARMED, MONOFUNCTIONAL, AND HYDROLYTICALLY STABLE DERIVATIVES OF POLY(ETHYLENE GLYCOL) AND RELATED POLYMERS FOR MODIFICATION OF SURFACES AND MOLECULES**		

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

DECLARATION UNDER 37 C.F.R. § 1.132

Sir:

I, Joe Milton Harris, declare that:

1. The statements contained herein are provided to demonstrate the patentability of the claims pending in the above-identified patent application, U.S. Application Serial No. 10/119,546. Claims pending in this application have been rejected in view of the asserted teachings of the primary reference, U.S. Patent No. 5,643,575 (Martinez).

2. I am currently the General Manager, Nektar Molecule Engineering, Nektar Therapeutics AL, Corporation (formerly Shearwater Corporation), the assignee of the subject

patent application. Prior to the acquisition of Shearwater Corporation by Inhale Therapeutic Systems, Inc., I held the positions of President, Chairman, and Chief Executive Officer of Shearwater Corporation (from 1992 to 2001).

3. I am also a named inventor in the subject patent application, U.S. Application Serial No. 10/119,546.

4. I received a B.S. degree in Chemistry from Auburn University in Auburn, Alabama in June, 1963 and a Ph.D. in Organic Chemistry from the University of Texas at Austin in Austin, Texas in 1969. I held a post as a post-doctoral research fellow with the National Institutes of Health at Princeton University from 1969 until 1970.

5. I currently hold the positions of Research Professor of Chemistry and Material Science at the University of Alabama in Huntsville and Affiliate Professor of Bioengineering at the University of Washington. I have held various professorships since 1970, and from 1991 to 1997 served as Distinguished Professor of Chemistry and Material Science at the University of Alabama in Huntsville.

6. I am the principal author or co-author of at least 160 journal articles and books on various scientific topics, most of which relate to organic and polymer chemistry. I am a named inventor on at least 20 issued U.S. patents.

7. I am currently active in research and development related to polyethylene glycol chemistry and its applications in biotechnology, medicine, drug delivery, and the like.

8. I have carefully reviewed the contents of U.S. Patent No. 5,643,575 ("the '575 patent";) and the accompanying Certificate of Correction. Claims in the parent of the instant patent application, Serial No. 10/119,546, were rejected in view of the teachings of the '575 patent. As I understand it, it is the Examiner's position that the recrystallization method in

Example 8 of the '575 patent inherently substantially removes polymeric impurities, and thus renders the Applicant's claims as non-novel and obvious in view of the '575 patent, when considered either alone or combined with other art of record.

9. I was aware of and personally supervised experiments conducted in Nektar's laboratories in an effort to (i) repeat Example 8 of the '575 patent, and (ii) examine effectiveness of conventional methods such as recrystallization in removing polymeric impurities from a branched polymer composition. The repeat of Example 8, referred to herein and in the accompanying **Exhibit A** as **Experiment 1**, was carried out to determine whether the reported branched polymer product, "U-LYS-PEG", purified by recrystallization, possessed a purity of the type recited in the Applicant's claims. The independent claims contained in the accompanying Preliminary Amendment recite a branched polymer of a purity sufficient for circulation in the bloodstream of a mammal. That is to say, the branched polymer of the invention is a purified polymer that is essentially absent detectable amounts of polymeric impurities (i.e., contains less than about five percent or so polymeric impurities).

10. As described in detail in **Exhibit A**, following the preparation described in Example 8 of the '575 patent resulted not in the reported structure, U-LYS-PEG, but rather resulted in unreacted starting material, mPEG-5K-NPC. This finding was confirmed by ^{1}H NMR analysis of the recovered recrystallized product (**FIG. 1**, bottom spectrum) when compared to the ^{1}H NMR spectrum of the mPEG-5K-NPC starting material (**FIG. 1**, top spectrum). Due to our recovery of unreacted starting material, we were unable, when following the teachings of Example 8, to examine the purity of the recrytallized polymer product, since the branched PEG lysine ester was not formed.

11. We then employed an alternative approach to examine the effectiveness of the recrystallization method of Martinez in removing polymeric impurities arising during the preparation of a branched polymer of the type recited in the Applicant's claims as set forth in detailed fashion in **Exhibit B**.

12. As stated in Exhibit B, the alternative method used to synthesize mPEG-2-LYS was essentially as described in the instant application, U.S. Serial No. 10/119,546, on pages 25 to 27. A greater than 2-fold molar excess of mPEG-succinimidyl carbonate was reacted with lysine monohydrochloride at pH ~8 to provide an aqueous reaction mixture containing crude mPEG-2-LYS. Following adjustment of the pH of the reaction mixture by addition of acid, the product was recovered by extraction into an organic phase, drying of the organic phase, and evaporation of the solvent to provide crude mPEG-2-LYS. A portion of the recovered crude mPEG-2-LYS, prior to purification, was withdrawn and saved for further analysis (Sample 1).

13. Recovered crude mPEG-2-LYS was then purified by recrystallization using the method described in the '575 patent. Crude mPEG-2-LYS was recrystallized from isopropyl alcohol, and the recrystallized product was then isolated by filtration, and dried under high vacuum (Sample 2). Sample 2 was set aside for further analysis.

14. For the sake of comparison, a portion of the recovered crude mPEG-2-LYS was also purified by aqueous chromatography, specifically, ion exchange chromatography using a DEAE-sepharose column as described on page 27 of the Applicant's application, U.S. Serial No. 10/119,546. Recovered, chromatographically purified mPEG-2-LYS (Sample 3) was then set aside for further analysis.

15. Samples 2 and 3 (recrystallized and chromatographically purified mPEG-2-LYS, respectively) were then analyzed by two different gel permeation chromatography (GPC) methods to examine their purity. In describing the results of this analysis, structures referred to herein are shown in Exhibit B, Table 5.

16. Referring to Exhibit B, Table 4, Sample 2 (the recrystallized product) exhibited a purity that was essentially unchanged from crude mPEG-2-LYS. As assessed by GPC, Sample 2 contained approximately 20% combined mPEG and mono-PEGylated product, mPEG-1-LYS,

and approximately 12% PEG-3. (Using GPC Method 1, we were unable to separate the product peak, mPEG-2-LYS, from PEG-3, so that the relative amount of product according to GPC Method 1 is artificially high). The recrystallized product contained only about 70% of mPEG-2-LYS, but was contaminated with sizable quantities of the polymeric impurities mPEG, mPEG-1-LYS, and PEG-3.

17. The recrystallization technique of the '575 patent does not purify the branched polymer, PEG-2-LYS, to any degree. With respect to polymeric contaminants, Sample 2 cannot be considered to be "purified" to any degree, let alone possess a purity sufficient for circulation in the bloodstream of a mammal.

18. Referring to Exhibit B, Table 4, Sample 3, as assessed by GPC, was essentially absent any detectable polymeric impurities, and contained only mPEG-2-LYS as the sole, detectable polymer species.

19. As stated herein and shown in the accompanying Exhibits, the recrystallized branched polymers of the '575 patent are not at all identical or even remotely similar in composition to the branched polymers of the instant application. The recrystallized polymers of the '575 patent contain sizable amounts of polymeric impurities, in contrast to the branched polymers claimed in the instant application, that have been successfully and purposefully purified to remove detectable amounts of polymeric impurities.

20. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; further, that these statements were made with the knowledge that willful false statements or the like so made are

punishable by fine or imprisonment, or both, under 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Joe Milton Harris

Date: July 11, 2003